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REMARKS

The Office action of March 3, 2003, has been carefully considered.

The Office action acknowledges Applicants' claim for foreign priority based upon an application filed in France, but notes that Applicants have not filed a certified copy of the French application. Applicants note, however, that the present application was filed under 35 USC 371, and that a certified copy of the French priority application has been filed with the International Bureau. Filing of a certified copy in the U.S. Patent and Trademark Office is not necessary under such circumstances, and in fact, PCT Rule 17.2a states that the National Office shall not ask an applicant to furnish such a copy.

Claims 1 through 3, 4 through 5 and 10 have been rejected under 35 USC 102(b) as anticipated by Helden et al.

The Helden et al reference discloses an aqueous phloroglucinol solution for developing printing plates buffered to a pH between 4 and 8 and containing 1 to 10% by volume of a water miscible organic solvent having molecular weight greater than 50.

Claims 1 through 10 have now been amended so that they are directed solely to a solid pharmaceutical composition

for oral administration of phloroglucinol comprising solid phloroglucinol in combination with a solid buffer system which, when the composition is placed in an aqueous medium, results in a pH in the aqueous medium between 3 and 7. As the Helden et al reference is directed only to an aqueous phloroglucinol solution which is buffered, and not to a solid pharmaceutical composition, the claimed invention is clearly distinguished from the cited reference.

In addition to the amendment of Claims 1 through 10, new Claims 11 through 28 have been added to the application. Claims 11 through 21 are directed to a method for administration of phloroglucinol to a human or animal in need thereof comprising administering the phloroglucinol in a composition in combination with a buffer. This is clearly not disclosed by Helden et al.

Claims 22 through 28 are directed to a dosage form for pharmaceutical administration of phloroglucinol comprising a therapeutically effective amount of phloroglucinol (about 80 mg in Claim 28) in combination with a buffer system capable of maintaining a pH between 3 and 7. This is also not disclosed by Helden et al, first because Helden et al discloses phloroglucinol in combination with an organic solvent which is not suitable for human administration, and second, because the

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examples of Helden et al disclose compositions containing amounts of phloroglucinol far in excess of a therapeutically effective amount, for example, 700 to 800 mg per 100 ml.

Withdrawal of this rejection is accordingly requested.

Claims 1 through 3 have been rejected under 35 USC 102(b) as anticipated by Kotz & Treichel, while Claims 1 through 9 have been rejected under 35 USC 102(b) as anticipated by the Alka-Seltzer reference. Both of these rejections have been based upon the allegation that Claim 1 as filed did not positively recite phloroglucinol, and only positively recited the buffer system. As the claims as amended all positively recite the presence of phloroglucinol, withdrawal of these rejections is requested.

Claims 1 through 10 have been rejected under 35 103 over Lafon taken with Blonde and further in view of the Alka-Seltzer reference. Applicants submit that the claimed invention is patentable over the cited combination of references.

Lafon has been cited by the Office action as showing pharmaceutical compositions containing phloroglucinol which are made in a Tyrode solution, which is a physiological saline solution containing, *inter alia*, sodium bicarbonate and sodium

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phosphate. A definition of Tyrode solution has been provided with the Office action, and it is noted from this definition that Tyrode solution is "used in physiological experiments, tissue cultures and tissue preservation, and to irrigate the peritoneal cavity." The "tissue preservation" use of Tyrode solution appears to be the purpose of its use in the Lafon reference, where it is stated that "[t]he duodena of these rats were taken and maintained alive in standard Tyrode solution..." (page 1, lines 77-79), and "[p]hloroglucinol was used in 1% aqueous solution and in 5% saturated solution and added to Tyrode liquid so as to have a total volume of 80 ccs. in each test tube." (page 1, line 86 through page 2, line 3).

Thus, Lafon uses Tyrode solution only in connection with *in vitro* administration of phloroglucinol, and apparently because the duodena of the rats were being maintained in Tyrode solution. While Lafon does state that phloroglucinol may be administered in combination with diluents or carriers, those diluents and carriers would appear to be such substances as glucose, lactose, starch, magnesium stearate, sodium lauryl sulfate, talc, gelatin, and wax. There is no disclosure or suggestion of administering phloroglucinol *in vivo* in combination with a buffer.

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The Blonde reference discloses sweetening compositions containing sodium saccharinate and phloroglucinol and discloses that such compositions may be prepared in lump form, apparently in an imitation of lump sugar. The lumps may also serve as carriers for various medicaments due to their rapid dissolution in water.

The Alka-Seltzer reference discloses a combination of citric acid, sodium bicarbonate and acetylsalicylate acid with saccharine sodium as sweetener and sodium benzoate as preservative. Alka-Seltzer maintains gastric pH between 5 and 7.

The Office action alleges that it would have been obvious for one of ordinary skill in the art to have modified the phloroglucinol containing compositions of Lafon and Blonde by adding phloroglucinol to the effervescent tablet taught by Alka-Seltzer. However, there is no specific reason given for doing so, other than the teaching of the invention that phloroglucinol should be administered together with a buffer to a pH between 3 and 7. Applicants have discovered that administration of phloroglucinol in combination with a buffer makes it possible to reduce the gastric acidity and surprisingly, to potentiate the anti-spasmodic activity of the phloroglucinol. Applicants have found that effervescent

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tablets buffered as defined by the invention have proven almost as effective as an intermuscular injection, and oral lyophilizates buffered as defined by the invention have also proven more effective than oral lyophilizates of the prior art which are not buffered.

The advantages of the invention are clearly set forth in the examples on pages 5 and 6 of the present specification in which an effervescent tablet of the invention containing 80 mg of phloroglucinol was compared with a distilled water control and an aqueous solution prepared from oral lyophilizates of the prior art. It is to be noted that the antispasmodic activity exhibited by the effervescent tablet was appreciably greater than that of the oral lyophilizate of the prior art.

A further test shown on pages 5 and 6 of the specification indicates that the effervescent phloroglucinol according to the invention is about as effective as intermuscular injection of phloroglucinol and far more effective than unbuffered phloroglucinol.

Thus, while the argument could be made that effervescent tablets are a standard method of administering a pharmaceutical, there is no disclosure or suggestion in the prior art that the effectiveness of phloroglucinol as an anti-

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spasmodic would be substantially enhanced by administration in combination with a buffer. As Applicants have shown a totally unexpected effect by administering phloroglucinol in combination with a buffer, it is submitted that Applicants have rebutted any allegation of *prima facie* obviousness by this combination of references, and withdrawal of the rejection is requested.

In view of the foregoing amendments and remarks, Applicants submit that the present application is now in condition for allowance. An early allowance of the application with amended claims is earnestly solicited.

Respectfully submitted,

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APPENDIX

IN THE CLAIMS:

1. (Twice Amended) [Pharmaceutical] A solid pharmaceutical composition for oral administration of phloroglucinol, comprising[,] solid phloroglucinol in combination with a solid buffer system, which, when the composition is placed in an aqueous medium, results in a pH in the aqueous medium [in a liquid state, a system which buffers the composition to a pH of between 3 and 7, or in a solid state, a system which, when placed in an aqueous medium, is capable of providing a buffer effect] between [pH] 3 and [pH] 7.

2. (Twice Amended) [Pharmaceutical] A solid pharmaceutical composition according to claim 1, wherein said buffer pH is between 4 and 6.

3. (Twice Amended) [Pharmaceutical] A solid pharmaceutical composition according to claim 1, in the form of [solutions, suspensions or syrups or in the form of] tablets, gelatin capsules, powders, granules or lyophilizates.

4. (Twice Amended) [Pharmaceutical] A solid pharmaceutical composition according to claim 1, wherein said buffer system [responsible for the buffer effect] comprises at least one organic acid and/or at least one salt of an organic

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acid in association with at least one strong base and/or at least one salt of a strong base.

5. (Twice Amended) [Pharmaceutical] A solid pharmaceutical composition according to claim 4, wherein said organic acid is selected from the group consisting of citric, tartaric, malic, lactic, acetic, glutaric, benzoic and adipic acids.

6. (Twice Amended) [Pharmaceutical] A solid pharmaceutical composition according to claim 4, wherein said base comprises sodium bicarbonate, sodium carbonate, calcium carbonate, magnesium carbonate, sodium hydroxide, potassium hydroxide, potassium bicarbonate or potassium carbonate.

7. (Twice Amended) [Pharmaceutical] A solid pharmaceutical composition according to claim 1, in the form of an effervescent solid galenical preparation.

8. (Twice Amended) [Pharmaceutical] A solid pharmaceutical composition according to claim 1, in the form of an effervescent tablet.

9. (Twice Amended) [Pharmaceutical] A solid pharmaceutical composition according to claim [1] 9, in the form of an effervescent tablet containing citric acid and sodium bicarbonate.

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10. (Twice Amended) Process for the preparation of a solid pharmaceutical composition according to claim 1, comprising formulating the phloroglucinol [in a liquid form with a system which buffers said liquid form to a pH of between 3 and 7, or] in a solid form with a solid buffer system which, when said solid [form] composition is placed in an aqueous medium, [is capable of providing a buffer effect] results in a pH between pH 3 and pH 7.

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